UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/932,834	09/18/97	PORUBEK	D 077319/0129

HM12/0729

FOLEY & LARDNER
3000 K STREET NW
SUITE 500
WASHINGTON DC 20007-5109

EXAMINER	
BERCH, M	
ART UNIT	**PAPER NUMBER**
1611	35

DATE MAILED: 07/29/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
08/932,834	Porubek
Examiner	**Group Art Unit**
Mark L. Berch	1611

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☐ expires _____ months from the mailing date of the final rejection.

b) ☐ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☒ Appellant's Brief is due two months from the date of the Notice of Appeal filed on *May 27, 1999* (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *Jul 14, 1999* has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:

☒ The proposed amendment(s):

☒ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☐ will not be entered because:

☐ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

☒ Applicant's response has overcome the following rejection(s):
See memo

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See memo

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: _____

Claims objected to: _____

Claims rejected: *1-7 and 9-27*

☐ The proposed drawing correction filed on _____ ☐has ☐has not been approved by the Examiner.

☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____.

☐ Other

MARK L. BERCH
PRIMARY EXAMINER
ART UNIT 1611

DETAILED ACTION

The explanation with regard to claim 14, species 3 is understood. In the future, it would be best to just amend in the proper manner, and state in the remarks that the amendment is tendered to deal with an earlier transcription error.

In the interests of advancing prosecution, the amendment is entered. However: a) the "or" in the next to last line of page 2 should not have been deleted, and b) while oxo was removed from the Q definition, claim 26, whose list includes oxo, was switched to a Q definition list. Deletion of oxo from claim 26, and reinstatement of the "or" is suggested.

Point 1 of the Final Rejection remains in part. The leading bond has been restored, but for some reason the "n" has been retained in the wrong place. See original claim 1 for correct formulation.

Point 2 of the Final Rejection remains. The replacement that the examiner refers to was done in the four times amended claim 6. This still needs to be fixed.

Point 3 still remains. The language has descriptive support in claim 3 but it is still not seen what these would look like. Applicants are urged to draw out what this would look like for e.g. glyceraldehydyl. The parent aldehyde is as depicted in the previous office action. Keep in mind that the group must be "attached by an oxygen atom ... by an ester linkage" This is not a problem for the amino acid, which by its very nature is an acid and thus can form esters, nor is it a problem for the finally fixed last term, which now must have one R_5 as O and is it thus automatically an ester

regardless of the nature of X or Q. But for glyceraldehydyl and other terms, which can be linked via an oxygen, but such a compound would be an ether, not an ester.

Points 4-6 are resolved.

The problem of the non-cleavable groups remains in part. See point 3 above. The ethers will not cleave. This issue now no longer applies to claim 14, as the two ethers were removed. Deletion of those carbohydrate choices will resolve this matter.

The how to use issue for lysofylline remains. The declaration is it noted and is it not persuasive. The declaration presents conclusions without supporting facts, and as such is it is it entitled to little or no weight, cf. *In re Etter*, 225 USPQ 1, 6; *In re Grunwell*, 203 USPQ 1055, 1059; *In re Buchner*, USPQ2d 1331; *In re Chilowski*, 134 USPQ 515,521; *In re Brandstadter*, 179 USPQ 286, 293-294, *In re Thompson*, 192 USPQ 275; *Ex parte George* 21 USPQ2nd 1058, 1062.

With regard to APPENDIX B (first, i.e. the Margolin paper), declarant says, "initial clinical trials were conducted, which bore out its therapeutic usefulness at this level." But this statement, and hence this declaration, is it not credible, because is it is it directly contradicted by the reference itself. It describes a large randomized trial to determine the ability of lysofylline to get around the problem that IL-2's toxicity limits the amount of it that you can use in treating certain cancers. The last paragraph of the abstract says that lysofylline "did not alter the toxicities of high dose i.v. IL-2 sufficiently to impact the overall dose density of IL-2." The copy of the reference provided to the PTO highlights isolated positive findings, but that does not change the

fact that the study failed to do what is it set out to do. Thus, page 570 says, "Specifically, LSF did not permit the administration of more IL-2 and did not substantially alter the toxicity of a fixed dose of IL-2." Moreover, this failure was not a fluke. Page 571 notes that "Other clinical studies attempting to modify the toxicities mediated by IL-2 and other inflammatory cytokines have also been disappointing." Indeed, the paragraph bridging columns of page 571 strongly suggests that the goal may not be achievable at all. Is it says that "is it is it likely that some if not all of the phenomena responsible for the multiorgan toxicities ... depend on the same biochemical pathways responsible for the antitumor effects." Thus, disrupting the toxicity would then disrupt the desired effect as well. The last sentence of the abstract suggests that success may require a higher dosage, a more potent agent than lysofylline or the addition of some additional "modulating agents" to the trials. This is clear evidence that more than routine experimentation remains to be done. Thus, while the declaration says (paragraph 7) that "a clinician could, via routine clinical procedures, select a suitable dosing scheme" that statement is it not consistent with the suggestion in the paper that this massive, multicenter study might have failed because a dose too low was chosen. If selecting a dose is it so routine, why would the authors have suggested that the dose might have been wrong?

APPENDIX B (second), C and D appear to be slides. It is impossible to tell what they are based on. APPENDIX E appears to be the abstract of some oral presentation. It is unclear what to make of this because the abstract does not come to any

conclusions, since both some positive specific and negative overall language is reported. The paper appears to identify subpopulations which may benefit, but unless the study set out to determine if that subpopulation was more amenable to the drug, that is not necessarily significant. It appears that there was only one treatment arm, and that arm did not differ from placebo.

It would be most helpful in overcoming this rejection if applicants would supply the published paper corresponding to APPENDIX B (second), C, D or E, assuming that the paper reaches a positive conclusion. Assuming that lysofylline has finally been made to work for something and that there was not undue experimentation involved, applicants would then only need to show that such utility was in the specification.

APPENDIX B (second), C, D or E are not included on the PTO 892 as there is not enough information to cite these, and APPENDIX B (second), C, and D do not appear to be publications but slides.

The above constitute all the remaining issues in this case.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718.

Mark L. Berch

Primary Examiner

Group 1610 - Art Unit 1611

July 23, 1999